LETTERS TO THE EDITOR

A clinical and genetic database for management of familial adenomatous polyposis

Cachon-Gonzalez *et al* (*J Med Genet* 1991;28:681–5) describe their experience with four linked DNA markers (π227, C11p11, YN5.48, and ECB27) flanking the familial adenomatous polyposis (FAP) locus. They conclude that "lod scores are sufficiently high to allow the use of these probes in presymptomatic diagnosis". In the absence of large bowel adenomas or extracolonic manifestations of the FAP gene, a Bayesian approach to risk assessment, incorporating age of onset and DNA data, may guide clinical screening policy. We have developed a computerised regional register for FAP (called 'MegaBASE/FAP') which facilitates both risk assessment and coordination of screening examinations for the extended families of index patients.

The core of the register software is the pedigree and this can be viewed on screen and printed out for use in the clinic. The main database contains information relating to administrative, screening, surgical, pathological, and genetic aspects of patient management, and this can be viewed and edited either on a text based screen or directly on the pedigree.

From the genotypes stored on each family member, input files for the LINKAGE[1] programs can be written automatically within the database, which also contains a built in age of onset curve specified as 20 liability classes. The time consuming and error prone manual creation of LINKAGE files is thereby avoided, making risk evaluation both simpler and more reliable.

Cachon-Gonzalez *et al* have suggested that closely linked markers might now be usefully incorporated in the modern management of FAP. By integrating clinical and genetic information our database has facilitated this development for families with FAP in our region.

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1 Lathrop GM, Lalouel JM. Easy calculations of lod scores and genetic risks on small computers. *Am J Hum Genet* 1984;36:460–5.

High proportion of twins in carriers of fragile X syndrome

Vogel[1] hypothesised that the extraordinarily high mutation rate in fragile X (fra X) syndrome can be reduced to conventional proportions if moderately increased fertility of clinically unaffected females (CUF) is assumed. The author concluded that this may be the result of an equilibrium between an increased reproduction rate in CUF and a decreased fertility in their affected relatives, and that equilibrium would require more than a doubling of the reproductive rate especially in CUF. An indicator of fertility in women is the dizygotic twinning rate, which is a consequence of an increase in ovarian stimulation by FSH (follicle stimulating hormone) and is influenced by maternal age and birth order.[2]

We have studied 65 women diagnosed as obligate carriers in 44 Spanish families with fra X syndrome in our Molecular Genetics Unit. In 10 of these carriers (15%), twins were observed in their progeny, with one carrier having three cases (total no = 12). Six cases were dizygotic and in the remaining six zygosity could not be determined. In total, the 65 carriers had 213 children and the twinning within this group was 1/18, in contrast with the twinning in our population of about 1/70 births.[3]

Similar data were reported by Fryns[4] in a study of the progeny of 144 obligate female carriers with a high incidence of twinning at 1/35 births (18/642), and Sherman and Turner[5] found that the twinning rate in their fra X carriers was 1/42 births (18/752), significantly higher than the twinning rates in their respective countries. Fryns concluded that these observed two to four-fold increases in the frequency of twinning among fra X carrier women may be evidence for a dysregulation of the cortico-hypothalamo-hypophyseal axis in fra X syndrome. In support of this, large ovaries and ovarian cysts have been reported in heterozygous fra X syndrome girls,[6–8] oligomenorrhoea and premature menarche have been reported in several related fra X carrier mothers in a large Dutch pedigree,[6] and at least two cases of precocious puberty have been reported in fra X girls.[9 10]

We think that our results are in agreement with the hypotheses of Vogel and Fryns and indicate once more the importance of performing more accurate investigations regarding ovarian stimulation, fertility, and fra X syndrome.

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3 *Demografía y Población. Partos Múltiples y Nacimientos 1979–1988*. Barcelona: Anuari Estadistic, 1988:41.
4 Fryns JP. The female and the fragile X syndrome. A study of 144 obligate female carriers. *Am J Med Genet* 1986;23:157–69.
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9 Buttler MG, Najjar JL. Do some patients with fragile X syndrome have precocious puberty? *Am J Med Genet* 1988;31:779–81.
10 Moore PSJ, Chudley AE, Winter JSD. True precocious puberty in a girl with the fragile X syndrome. *Am J Med Genet* 1990;37:265–7.

BOOK REVIEWS

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (Mastercard, Visa, or American Express) stating card number, expiry date, and full name.

International Nomenclature of Diseases. Vol VI. **Metabolic, Nutritional and Endocrine Disorders.** (Pp 464; SFr 25.00.) London: The Council for International Organizations of Medical Sciences and the World Health Organization. 1991.

It is a difficult but very important job to define disease names that can be used internationally and which are unlikely to change rapidly. The Council for International Organizations of Medical Sciences and the World Health Organization, together with their many eminent advisors, are to be congratulated on doing just that. This is volume VI and the first to be of particular interest to geneticists. Further volumes are planned and these will include ones on musculoskeletal disorders, immune disorders, and diseases of the eye. *International Nomenclature of Diseases* is complementary to the *WHO Classification of Diseases* and neither replaces nor duplicates it.

For inclusion in these directories, a disease must be a well defined pathological entity, and the name for it should be simple, unambiguous, and descriptive. I am thankful that the use of numbers, initials, and eponyms are avoided where possible, although they are listed under synonyms. Older names for enzymes are also listed under synonyms and are indexed, so there is no difficulty about learning to use the correct name. There are brief notes on each disease and these are a model of precision and clarity.

The wide scope of this book is shown by its divisions into sections on inborn errors of metabolism (all genetic), disorders of steroid and endocrine metabolism, disorders of red cells and of haemoglobin, disorders of platelets and clotting, amyloidoses, collagenoses, muscular dystrophies, nutritional defects, diabetes mellitus with its syndromes, and endocrine tumours. There are also included some benign metabolic conditions so that they may be identified as 'non-diseases'.

The authors recognise that individual enzyme defects will be caused by different genes, and even by genes at different loci. Therefore they have chosen the enzyme defect as a basis for naming most of the diseases in this book. This is of great practical value. Only in the amyloidoses are DNA mutations included in the definition. It seems a good idea to use DNA mutations rarely, since they are being recognised at such a rate that disease names which incorporate them will have to be modified and expanded in the near future. It is helpful to a non-biochemist to have the biochemical basis of disease so clearly and correctly described in this handbook. As an example of how the editors are obsessed with correctness, the reader is even shown how to write glucose 6-phosphate and glucose-6-phosphatase.

The names of diseases listed here are numbered by intervals of ten, from 10 to 7570. Are these as useful for geneticists as McKusick's *Mendelian Inheritance in Man* (MIM)? They are certainly more logical as explanations of the clinical disease as they are largely based on function and gene product. Of course the MIM catalogue is more comprehensive and contains unexplained syndromes and diseases including those that have appeared only once. Nevertheless, the clarity and logic of this volume VI of the *International Nomenclature of Diseases* commend themselves to clinical geneticists, particularly for those studying or reporting patients with biochemical errors. It is a remarkable achievement to have produced a nomenclature of these metabolic and endocrine disorders that can be used throughout the world, and I eagerly await future volumes.

S BUNDEY

Molecular Mechanisms and their Clinical Application in Malignancies. Ed D E Bergsagel, T W Mak. (Pp 270; $49.95.) San Diego: Academic Press. 1991.

This book is the publication of the twelfth annual Bristol-Myers Squibb Symposium on Cancer Research. The book covers the four sections of the two day symposium: the genetic basis for neoplasia, genetic abnormalities in specific tumours, genetic basis of the cellular response to therapy, and application of molecular biology to clinical treatment. The book aims to make available current ideas and knowledge from some of the foremost investigators in cancer research to a wider group of scientists and particularly clinicians. The result is a very varied assortment of molecular and cell biology in and around the cancer field. The wide range of contributors gives the reader an insight into linkage and cloning studies, resistance to anticancer drugs, possible inherited enzymic determinants in lung cancer, functions of interleukin, regulation of transcription, biology of oncogenes, loss of tumour suppressor genes, retinoid and thyroid hormone receptors, and T cell receptor genes in malignant disease.

The inevitable tendency to report current knowledge leaves the information, already out of date in some chapters, suspended in time without the benefit of history. For instance the cloning of the genes for type 1 neurofibromatosis and adenomatous polyposis coli came too late for publication. Some chapters cater for a limited understanding of the field (molecular genetic analysis of the phakomatoses) whereas others launch straight into jargonese. There are good chapters on retinoblastoma and cachectin in the biology of cells which are clear, concise, and well structured. There is very limited content on clinical application of the knowledge except towards the end of the book (structural design in antitumor compounds). The book may be useful to a wide range of people in or around the cancer field. There could have been a better finished product with more active editing including that of the format which was not consistent. Scientists in the research field are more likely to benefit than clinicians unless they too have an active research interest.The book is unlikely therefore to fulfil one of its primary objectives of keeping clinicians abreast of the current research. Such an aim could only have been achieved by simplifying the data and giving more explanation. This would then have made the finished product less valuable to the researcher.

D G R EVANS

Molecular Genetic Approaches to Neuropsychiatric Diseases. Ed Jurgen Brosius, Robert T Fremeau. (Pp 493; $69.95.) New York: Academic Press. 1991.

This book sets out to provide series of up to date reviews of the application of molecular genetic techniques to the study of a variety of 'neuropsychiatric diseases'. Part I is concerned with methodology. The first two chapters review recent technological advances in molecular genetics and the third chapter describes the principles of human genetic linkage analysis. Part II contains three chapters on the molecular genetics of metabolic diseases covering mitochondrial diseases, lysosomal storage diseases, and Lesch-Nyhan syndrome. Part III covers the molecular genetics of neuromuscular diseases and includes chapters on Duchenne and Becker muscular dystrophy and on myotonic muscular dystrophy. Part IV considers the molecular genetics of neoplastic and viral diseases of nervous tissue and includes chapters on neurofibromatosis types 1 and 2, retinoblastoma, and viral diseases of the nervous system. Part V contains chapters on Alzheimer's disease and schizophrenia. Part VI is concerned with mental retardation and contains chapters specifically on the fragile X syndrome and an overview of molecular genetics and mental retardation. The final part is concerned with animal models.

It can be seen from the book's contents that the Editors' concept of 'neuropsychiatric diseases' is a broad one and the book would have perhaps been better entitled 'Molecular genetic approaches to neurological and psychiatric diseases'. In general the standard of the chapters is extremely high and the Editors have managed to recruit a distinguished collection of 'big name' authors. The book suffers from two of the problems that beset multiauthor texts in this field. First, there is some repetition of basic concepts and also in the coverage of specific diseases, for example, both Tay-Sachs disease and fragile X syndrome have chapters dedicated to them yet are also covered in some detail in the chapter on mental retardation. No doubt one of the drawbacks of having distinguished authors is that it makes editorial pruning more difficult! Second, a number of the chapters have already been overtaken by recent advances, for example, Alzheimer's disease, fragile X syndrome, myotonic dystrophy, and neurofibromatosis 1. The focus of the book is very much on molecular biological techniques and clearly shows how these have led to remarkable advances in understanding a wide range of diseases affecting the nervous system. In their preface, the editors claim that this book is "intended to benefit a broad audience ranging from graduate students to established investigators, and from clinical neurologists and psychiatrists to molecular biologists interested in neuropsychiatric diseases". They also hope that it will "convey the sense of excitement and promise that accompanies on-going research". In my opinion it fulfils these claims admirably and I strongly recommend it.

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